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(54) **Oral dosage forms of omega-3 polyunsaturated acids**

(57) Omega-3 polyunsaturated acids, especially EPA and/or DHA, in free acid form or as pharmaceutically acceptable salts are presented in enteric dosage forms to overcome the problems of belching and the risk of oxidation in the stomach associated with the oral administration of said acids. The acids can be used alone or with other active principles, especially linoleic acid, gamma-linolenic acid, and/or dihomo-gamma-linolenic acid. Preferably, the enteric dosage form is an enterically coated capsule such as a soft or, especially, hard gelatine capsule.

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ORAL DOSAGE FORMS OF OMEGA-3 POLYUNSATURATED ACIDS

The present invention relates to the oral administration of omega-3 polyunsaturated acids especially, but not exclusively, all-cis-5,8,11,14,17--  
05 eicosapentaenoic acid (i.e. all-cis-fatty acid 20:5 omega-3; EPA) and/or 22:6 omega-3-docosahexaenoic acid (DHA). In particular, it provides enteric dosage forms of omega-3 polyunsaturated acids.

It has been known for many years that the low  
10 occurrence of atherosclerotic cardiovascular diseases amongst Greenland Eskimos and the low mortality rate of cardiovascular patients in Scandinavia is attributable to the consumption of relatively high amounts of fish oil. The relevant active ingredients in fish oil have  
15 been identified as the omega-3 polyunsaturated acids EPA and DHA, which are present in their triglyceride and/or other esterified forms. The use of EPA in free acid form or as a pharmaceutically acceptable salt, ester or amide is disclosed in GB-A-1604554 and GB-A--  
20 2033745. Further, US-A-4097602 disclosed the inhibition of blood platelet aggregation by administration of EPA in its free acid form or as a salt or lower alkyl ester. More recently, US-A-4526902 disclosed the prophylaxis of thrombo-embolic conditions by simultaneous  
25 administration of EPA and/or DHA with one or more of linoleic, gamma-linolenic or dihomogamma-linolenic

acid. The said acids can be present as the free acid or as pharmaceutically acceptable salts, or esters or amides thereof.

Formulations used or proposed for the  
05 administration of EPA and/or DHA include oral, rectal, topical, vaginal, intrapulmonary and parenteral formulations. Usually, oral formulations have been employed, especially soft gelatine capsules. However, a problem associated with such oral administration is  
10 belching resulting in an unpleasant fishy smell and taste following disintegration or dissolution of the oral formulation in the stomach. Such a problem previously was well established in the administration of cod liver oil capsules which, because of the vitamin  
15 A and D content of the oil, have been used for many decades as a dietary supplement.

When EPA and/or DHA are administered in the form of a derivative thereof, usually an alkyl ester or triglyceride, it must be converted into the free fatty  
20 acid before being absorbed by the body. The conversion of ester is carried out in the stomach by the pancreatic enzyme Lipase. However, not all patients produce sufficient Lipase to properly convert the derivative into free fatty acid form. For example, the  
25 production of Lipase may be reduced, or even eliminated, as a result of disease or due to alcohol, smoking, stress etc. Accordingly, there is good reason to prefer to use EPA and/or DHA in the free acid form.

However, because of their polyunsaturation the free fatty acids are prone to rapid oxidation, which problem is not encountered with the esters. Although antioxidants, e.g. gamma-tocopherol, are used to  
05 prevent or at least reduce oxidation, the present Inventor suspects that significant oxidation of the acid takes place in the stomach thereby reducing the availability of the fatty acids.

The teaching and practice in the art to date has  
10 been that the free acid is administered orally in the same manner as the esters.

The present Inventor has appreciated that the long standing problem of belching with the accompanying fishy smell and taste associated with the oral  
15 administration of EPA and/or DHA and the risk of oxidation in the stomach can simply and readily be overcome by use of an enteric dosage form (i.e. a dosage form which, when taken orally, will pass through the stomach substantially without release of the active  
20 principle but which will release the active principle in the intestine). Although enteric dosage forms are widely used, there was, to the best of our knowledge, no previous proposal that omega-3 polyunsaturated free acids should be presented in enteric dosage form and it  
25 had not been appreciated that there was any reason or

advantage arising from the use of that form. Thus, the present invention resides in the enteric presentation of omega-3 polyunsaturated free acids as distinct from enteric dosage forms in general.

05       The present invention provides an enteric dosage form containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof. Further, the invention provides the use of said enteric dosage  
10 forms in the treatment or prophylaxis of thrombo-- embolic conditions. It also provides said enteric dosage forms for the treatment of other conditions for which omega-3 polyunsaturated acids in their free or precursor form, such as their glyceride or alkyl  
15 esters, are indicated. Such conditions include rheumatoid arthritis, diabetes mellitus, migraine, psoriasis, cancer, and hypercholesterolaemia and as a dietetic.

As indicated previously, it is preferred that the  
20 omega-3 polyunsaturated acid is EPA, DHA or a mixture thereof. It is present in free acid form or as a pharmaceutically acceptable salt thereof and can be present as the sole active principle or with other active principles, especially linoleic acid, gamma--  
25 linolenic acid and/or dihomo-gamma-linolenic acid in free acid or salt form.

Omega-3 polyunsaturated acids are readily oxidised and hence an antioxidant usually will be present. The presently preferred antioxidant is gamma-tocopherol but other pharmacologically acceptable antioxidants can be  
05 used, for example butylated hydroxy anisole, butylated hydroxy toluene, propyl gallate or a quinone.

The enteric dosage form may also contain one or more pharmaceutically acceptable excipients depending upon the precise nature of the dosage form.

10 Suitably, the enteric dosage form can be an enterically coated tablets containing the omega-3 polyunsaturated acid in a microencapsulated form or loaded on a suitable absorbent. However, it is preferred that the enteric dosage form is an  
15 enterically coated capsule, especially a soft or, more especially, hard gelatine capsule.

Enteric coatings are widely used in the pharmaceutical industry and are formed of substances which are relatively insoluble in the acid medium of  
20 the stomach but disintegrate in the medium of the small intestine. Suitable enteric coatings include cellulose acetate phthalate and polymethacrylate.

Usually, the omega-3 polyunsaturated acid will be administered in a daily dosage of 20 to 50 mg/kg,  
25 especially 30-40 mg/kg. The actual dose will vary

depending inter alia on the identity of the omega-3 polyunsaturated acid and the nature and degree of the disorder being treated. Usually, each unit dose will contain 250 to 1000 mg, especially 400 to 800 mg.

05        The following is a description, by way of example only, of a presently preferred embodiment of the invention.

Example

Transparent hard gelatine capsules (size 0),  
10    consisting of 14% water and 86% gelatine were each filled with 500 mg of a fish oil concentrate (EPACHOL 600) supplied by Messrs. EPA Limited (Windsor, Ontario, Canada). The concentrate contains about 32% by weight free EPA, about 28% by weight free DHA and 0.02% by  
.15    weight gamma-tocopherol. It does not contain any cholesterol, cetoleic acid or saturated fatty acids and is an oily liquid of brown colour having a characteristic odour. It has the following physico-chemical properties:-

20	acid value	160
	iodine value	340
	peroxide value	3
	saponification value	190
	saponifiable matter	1.25
25	relative density	0.935
	refractive index	1.49

The filled gelatine capsules were placed in a

coating tower where they were carried in a heated (55°C) air stream whilst being sprayed with an enteric coating solution. The coating solution had the following composition by weight:-

05	cellulose acetate phthalate BPC	40 mg
	ethyl phthalate BPC	12 mg
	methylene chloride	616 mg
	ethyl alcohol 95% I.B.	128 mg.

Sufficient coating solution was applied to provide a  
10 theoretical coating of 6 mg/2, which is an excess of  
that theoretically required in order to allow for  
losses during the coating process.

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CLAIMS

1. An enteric dosage form containing as an active principle an omega-3 polyunsaturated acid in free acid form or as a pharmaceutically acceptable salt thereof.
2. An enteric dosage form as claimed in Claim 1, wherein said acid is EPA, DHA or a mixture thereof.
3. An enteric dosage form as claimed in Claim 1 or Claim 2, wherein said acid is present in free acid form.
4. An enteric dosage form as claimed in any one of the preceding claims, wherein said acid or salt is present as the sole active principle.
5. An enteric dosage form as claimed in any one of Claims 1 to 4, wherein said acid or salt is present with another active principle selected from linoleic acid, gamma-linolenic acid, and/or dihomo-gamma-linolenic acid in free acid form or as a pharmaceutically acceptable salt thereof.
6. An enteric dosage form as claimed in any one of the preceding claims containing an antioxidant amount of gamma-tocopherol.
7. An enteric dosage form as claimed in any one of the preceding claims which is an enterically coated tablet containing the said acid or salt in a microencapsulated form or loaded on an absorbent.

8     An enteric dosage form as claimed in any one of Claims 1 to 6 which is an enterically coated capsule.

9     An enteric dosage form as claimed in Claim 8, wherein the capsule is a soft gelatine capsule.

05 10   An enteric dosage form as claimed in Claim 8, wherein the capsule is a hard gelatine capsule.

11   An enteric dosage form as claimed in any one of the preceding claims, wherein each unit dose contains 250 to 1000 mg of said omega-3 acid or salt.

10 12   An enteric dosage form as claimed in Claim 11, wherein each unit dose contains 400 to 800 mg of said omega-3 acid or salt.

13   An enteric dosage form substantially as hereinbefore described in the Example.

15 14   The use of an enteric dosage form as claimed in any one of the preceding claims in the treatment or prophylaxis of thrombo-embolic conditions.

15   The use of an enteric dosage form as claimed in any one of Claims 1 to 13 for the treatment of  
20 rheumatoid arthritis.

16   The use of an enteric dosage form as claimed in any one of Claims 1 to 13 for the treatment of diabetes mellitus.

17   The use of an enteric dosage form as claimed in  
25 any one of Claims 1 to 13 for the treatment of migraine.

18 The use of an enteric dosage form as claimed in  
any one of Claims 1 to 13 for the treatment of  
psoriasis.

19 The use of an enteric dosage form as claimed in  
05 any one of Claims 1 to 13 for the treatment of cancer.

20 The use of an enteric dosage form as claimed in  
any one of Claims 1 to 13 for the treatment of  
hypercholesterolaemia.

21 The use of an enteric dosage form as claimed in  
10 any one of Claims 1 to 13 as a dietetic.

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